

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

B7

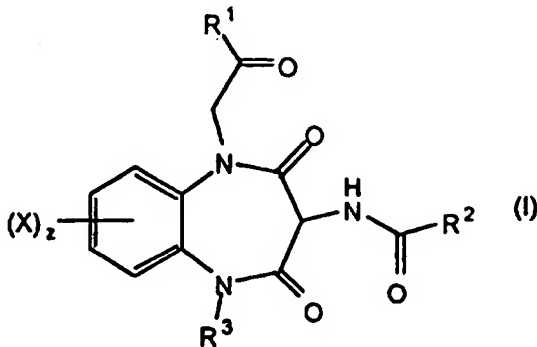
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 38/22		A1	(11) International Publication Number: WO 96/11701
			(43) International Publication Date: 25 April 1996 (25.04.96)
(21) International Application Number: PCT/US95/12829		(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).	
(22) International Filing Date: 13 October 1995 (13.10.95)		Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(30) Priority Data: 9420748.7 14 October 1994 (14.10.94) GB			
(71) Applicant (for all designated States except US): GLAXO WELLCOME INC. [US/US]; 5 Moore Drive, Research Triangle Park, NC 27709 (US).			
(72) Inventor; and (75) Inventor/Applicant (for US only): SUGG, Elizabeth, Ellen [US/US]; Glaxo Wellcome Inc., 5 Moore Drive, Research Triangle Park, NC 27709 (US).			
(74) Agents: LEVY, David, J.; Glaxo Wellcome Inc., Intellectual Property Dept., Five Moore Drive, Research Triangle Park, NC 27709 (US) et al.			

(54) Title: ENTERIC COATED COMPOSITIONS OF 1,5-BENZODIAZEPINE DERIVATIVES HAVING CCK ANTAGONISTIC OR AGONISTIC ACTIVITY

(57) Abstract

A pharmaceutical formulation in solid dosage form for oral administration which comprises a compound of general formula (I) or a physiologically salt thereof together with one or more pharmaceutically acceptable carriers wherein the formulation is encased in an enteric coating or capsule.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

**ENTERIC COATED COMPOSITIONS OF 1,5-BENZODIAZEPINE DERIVATIVES
HAVING CCK ANTAGONISTIC OR AGONISTIC ACTIVITY**

5 This invention relates to pharmaceutical compositions containing novel 1,5-benzodiazepine derivatives which exhibit agonist activity for CCK-A receptors thereby enabling them to modulate the hormones gastrin and cholecystokinin (CCK) in mammals.

10 Cholecystokinins (CCK) and gastrin are structurally related peptides which exist in gastrointestinal tissue and in the central nervous system. Cholecystokinins include CCK-33, a neuropeptide of thirty-three amino acids in its originally isolated form, its carboxyl terminal octapeptide, CCK-8 (also a naturally occurring neuropeptide), and 39- and 12-amino acid forms. Gastrin occurs in 34-, 17- and 14- amino acid forms, with the minimum active
15 sequence being the C-terminal tetrapeptide, Trp-Met-Asp-Phe-NH₂ (CCK-4) which is the common structural element shared by both CCK and gastrin.

CCK and gastrin are gastrointestinal hormones and neurotransmitters in the neural and peripheral systems and perform their respective biological roles
20 by binding to particular receptors located at various sites throughout the body. There are at least two subtypes of cholecystokinin receptors termed CCK-A and CCK-B and both are found in the periphery and in the central nervous system.

25 The CCK-A receptor, commonly referred to as the "peripheral-type" receptor, is primarily found in the pancreas, gallbladder, ileum, pyloric sphincter and on vagal afferent nerve fibers. Type-A CCK receptors are also found in the brain in discrete regions and serve to provide a number of CNS effects. Due to the ability of CCK-8 and Type-A CCK-selective agonists to suppress food
30 intake in several animal species, considerable interest has been generated toward the development of new substances which function as Type-A receptor-selective CCK agonists in order to serve as anorectic agents.

The CCK-B or gastrin receptors are found in peripheral neurons,
35 gastrointestinal smooth muscle and gastrointestinal mucosa, most notably in parietal cells, ECL cells, D cells and chief cells. CCK-B receptors also predominate in the brain and have been implicated in the regulation of anxiety, arousal and the action of neuroleptic agents.

2

U.S. Patent No. 4,988,692, to Gasc, et al. describes a group of 3-acylamino 1-alkyl-5-phenyl 1,5-benzodiazepine derivatives which behave as cholecystokinin antagonists to reverse or block the effects of the endogenous hormone at its receptors.

5

US Patent No. 4,490,304 and PTC applications No's WO90/06937 and WO91/19733 describe peptide derivatives that exhibit CCK-A agonist activity. Such compounds have been disclosed for appetite regulation as well as the treatment and/or prevention of gastrointestinal disorders or disorders of the central nervous in animals and, more particularly, humans.

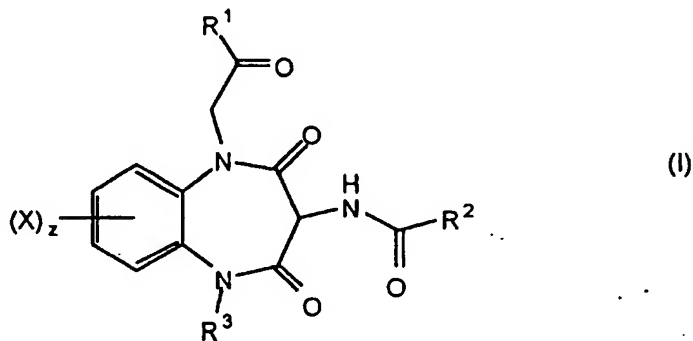
10

We have now discovered that the bioavailability following oral administration of a novel group of 3-amino 1,5-benzodiazepine compounds which exhibit a agonist activity for the CCK-A receptor may be significantly increased if the compound is administered in a solid dosage form the outer layer of which is an enteric coating or shell.

15

The present invention thus provides a pharmaceutical formulation in solid dosage form for oral administration which comprises a compound of the general Formula (I)

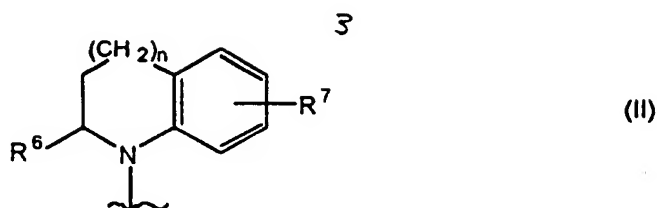
20



and physiologically salts and solvate thereof wherein:

25 X is either hydrogen, trifluoromethyl, alkyl, C₁₋₄alkylthio, -O(C₁₋₄alkyl) or halogen;

R¹ is either Formula II or -NR⁴R⁵;



R² is either:

- 5 (1) a heterocycle linked at its 2- position and selected from pyrrole, tetrahydropyrrole, indole, benzofuran, thiophene, benzothiophene, indoline, quinoline or 4-oxobenzopyran and wherein said pyrrole, tetrahydropyrrole, indole or indoline may optionally be substituted on the ring nitrogen thereof by the group R⁸ as defined hereunder and said indole, indoline, quinoline, benzofuran, benzothiophene or 4-oxo-benzopyran may optionally be substituted in the benzo ring thereof by the group R⁹ as defined hereunder or
- 10
- 15 (2) phenyl or phenyl mono- or disubstituted independently with halogen, hydroxy, cyano, carboxy, -O(C₁₋₄alkyl), -O(CH₂C₆H₅), -COO(C₁₋₄alkyl), amino, dimethylamino, -NHR¹⁰, 1-pyrrolidinyl or tetrazolyl; or
- 20 (3) pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, -O(C₁₋₄ alkyl), -O(CH₂C₆H₅), -COO(C₁₋₄alkyl), amino or dimethylamino; or
- 25 (4) -NHR¹¹ where R¹¹ is defined hereinunder or R¹¹ is 7-indazolyl containing a group R¹⁰ at the N-1 position;

R³ is hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl or phenyl mono- or disubstituted independently with halogen;

- 30 R⁴ is independently C₃₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆alkenyl, phenyl, -(CH₂)_pCN or -(CH₂)_pCOO(C₁₋₄alkyl) and R⁵ is independently C₃₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆alkenyl, benzyl, phenyl or phenyl mono- or disubstituted independently with C₁₋₃alkyl optionally substituted with 1 or more fluorine atoms, cyano, hydroxy, dimethylamino, -O(C₁₋₄alkyl), -O(CH₂C₆H₅), -
- 35 NH(C₁₋₄alkyl), -COO(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂ pyrrolidino, morpholino or

halogen or R⁴ is C₁₋₂alkyl and R⁵ is phenyl substituted at the 2- or 4- position with chloro, methyl, methoxy or methoxycarbonyl;

R⁶ is hydrogen or methyl;

5

R⁷ is hydrogen, hydroxy, fluoro, dimethylamino, -O(C₁₋₄alkyl) or -O(CH₂C₆H₅);

R⁸ is -(CH₂)_bCOOH;

10

R⁹ is methyl, chloro, nitro, hydroxy, methoxy or -NHR¹⁰;

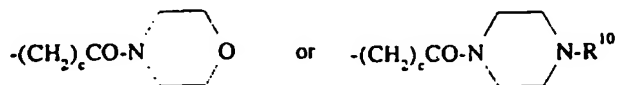
R¹⁰ is hydrogen, acetyl, C₁₋₄alkyl, -SO₃H, -SO₂CH₃, -SO₂CF₃ or -SO₂C₆H₅, C₁₋₄alkoxycarbonyl;

15

R¹¹ is phenyl or phenyl mono- or disubstituted independently with fluorine, trifluoromethoxy, C₁₋₄alkylthio, -(CH₂)_cCOOH, -(CH₂)_cCOO(C₁₋₄alkyl), -(CH₂)_cSCH₃, -(CH₂)_cSOCH₃, -(CH₂)_cSO₂CH₃, -(CH₂)_cCONH₂, -SCH₂COOH, -CONH(SO₂CH₃), -CONH(SO₂CF₃), -(CH₂)_cN(C₁₋₄alkyl)₂, -(CH₂)_cNH(SO₂CF₃), -(CH₂)_cN(SO₂CF₃)(C₁₋₄alkyl), -(CH₂)_cSO₂NHCO(C₁₋₄alkyl), -(CH₂)_cSO₂N(C₁₋₄alkyl)CO(C₁₋₄alkyl), -(CH₂)_cCONHSO₂(C₁₋₄alkyl), -(CH₂)_cCON(C₁₋₄alkyl)SO₂(C₁₋₄alkyl), -(CH₂)_cOR¹², -(CH₂)_cNHR¹⁰ or phenyl monosubstituted with -(CH₂)_c(tetrazolyl), -(CH₂)_c(carboxamidotetrazolyl) or -(CH₂)_c(pyrrolidinyl) or R¹¹ is selected from
 20 pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, -O(C₁₋₄ alkyl), amino, dimethylamino, -NHR¹⁰;

25

R¹² is hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, -CH₂C₆H₅, -CH₂COOH, -CH₂CONH₂, -CH₂CONH(C₁₋₄alkyl), -CH₂CON(C₁₋₄alkyl)₂ or
 30



z is 1 or 2;

35

n is 1 or 2;

p is an integer from 1-4;

b is an integer from 0-3; and

c is 0 or 1.

5

together with one or more pharmaceutically acceptable carriers, wherein the formulation is encased in an enteric coating or capsule.

10 Conveniently the formulation according to the invention is in the form of a tablet coated with a conventional enteric coating. Alternatively the formulation according to the invention may be presented in the form of a capsule the shell of which is made from enteric material or is coated with an enteric material.

15 In the context of this application it will be understood that the term enteric coating or material refers to a coating or material that will pass through the stomach essentially intact but will rapidly disintegrate in the small intestine to release the active drug substance.

20 The tablets and capsules for oral administration may contain conventional excipients such as binding agents, (for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone), fillers (for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol), lubricants (for example, magnesium stearate, stearic acid, talc polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycollate) or wetting agents, such as sodium lauryl sulphate. The enteric coatings may be applied to the tablets and/or capsules according to methods well-known in the art.

30 Suitable enteric coatings for use in the invention will be these coatings known to those skilled in the art. Such coatings include cellulose acetate phthalate, polyvinyl acetate phthalate, shellac, styrene maleic acid copolymers, methacrylic acid copolymers and hydroxypropyl methyl cellulose phthalate. The said coatings may also contain a plasticizer and or
35 a dye.

6

In the compounds of formula (I) when R^1 represents the group of Formula (II), examples of such a group include those wherein R^6 is hydrogen or more particularly methyl, R^7 is hydrogen, hydroxyl, methoxy, or fluorine, and n is 1. In the compounds of formula I when R^1 represents the group of Formula (II),
5 examples of such a group include those wherein R^6 is hydrogen or more particularly methyl, R^7 is hydrogen, hydroxyl, methoxy, or fluorine, and n is 1.

When R^1 represents the group NR^4R^5 , examples of suitable groups include those wherein R^4 represent C_{3-6} alkyl, such as propyl or isopropyl, cyclohexyl or phenyl and R^5 represents C_{3-6} alkyl, benzyl or phenyl
10 optionally substituted in the para- position by hydroxy, dimethylamino methoxy, trifluoromethyl, fluorine, pyrrolidino or morpholino. Within this group, particularly useful R^1 groups include those wherein R^4 is propyl and, more particularly, isopropyl and R^5 represents phenyl or phenyl substituted in
15 the para-position by groups selected from hydroxy, methoxy dimethylamino, fluorine, or morpholino.

Examples of particularly suitable R^1 groups include those wherein R^1 is the group of Formula (II) wherein R^6 is methyl, n is 1 and R^7 is hydrogen, hydroxy, fluorine or methoxy or R^1 is the group NR^4R^5 wherein R^4 is propyl
20 or isopropyl and R^5 is phenyl optionally substituted in the para position by a group selected from hydroxy, methoxy, fluoro, dimethylamino, pyrrolidino or morpholino.

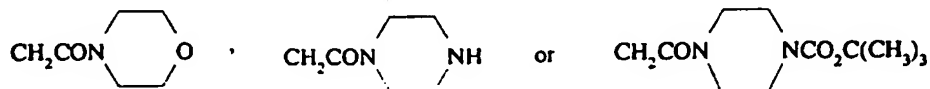
25 When R^2 represents a group selected from indole, indoline, benzofuran, benzothiophene, quinoline or 4-oxobenzopyran, the optional substituent R^9 is conveniently a group selected from hydrogen, methyl, methoxy, hydroxy, nitro or amino and, where appropriate, the optional substituent on nitrogen, (R^8), is $-CH_2CO_2H$.

30

When R^2 is an optionally substituted phenyl group, this is conveniently phenyl or phenyl substituted by one or two groups, which may be the same or different and selected from chlorine, fluorine, amino, hydroxy or carboxyl.

35 When R^2 represents the group NHR^{11} , R^{11} is conveniently phenyl (optionally substituted by fluoro, hydroxy, amino, dimethylamino, trifluoromethylsulphonylamino, C_{1-4} alkoxy carbonyl, carboxy, 1H-tetrazol-5-

yl, acetyl amino or OR¹² wherein R¹² represents hydrogen, methyl, benzyl, CH₂CO₂H, CH₂CONH₂, CH₂CONHCH₃, CH₂CON(CH₃)₂



5) or a 7-indazolyl group wherein the N-1 substituent, (R¹⁰), is hydrogen.

When R¹¹ is a mono substituted phenyl group, the substituted is conveniently in the meta- position.

- 10 Examples of particularly suitable R² groups includes indole, benzofuran, thiophene, benzothiophene, indoline, quinoline, 4-oxobenzopyran, an optionally substituted phenyl group or the group NHR¹¹. Conveniently, R² is selected from the group indole, indoline or benzofuran, an optionally substituted phenyl group or the group NHR¹¹. More particularly, R² represents an indole, an optionally substituted phenyl or NHR¹¹.
- 15

When R³ represents C₁₋₆ alkyl, examples of suitable groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl or isoamyl.

- 20 When R³ represents C₃₋₆ cycloalkyl, examples of suitable groups include cyclopropyl, cyclopentyl or cyclohexyl.

When R³ represents phenyl, mono or disubstituted by independently with halogen, examples of suitable groups include those wherein the halogen substituent is fluorine e.g., 2-fluorophenyl or 4 fluorophenyl.

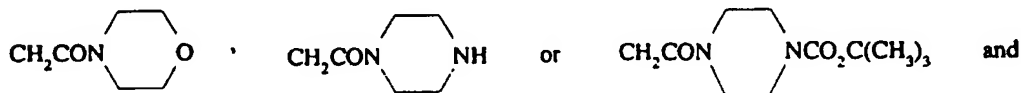
25

Examples of particularly suitable R³ groups include hydrogen, methyl, cyclohexyl, 2-fluorophenyl or phenyl, and more particularly, phenyl.

- 30 A particularly useful group of compounds for use in the formulations according to the invention include those wherein R¹ represents the group of Formula (II) wherein R⁶ is methyl, n is 1 and R⁷ is hydrogen, fluorine, hydroxy or methoxy, or more particularly NR⁴R⁵ wherein R⁴ is propyl or isopropyl and R⁵ is phenyl optionally substituted in the para position by a group selected from hydroxy, methoxy, fluoro, dimethylamino or monopholino; R² represents phenyl (optionally substituted independently by one or two groups selected from chlorine, fluorine, hydroxy, amine or
- 35

carboxy), NHR^{11} wherein R^{11} represents phenyl (optionally substituted by amino, dimethylamino, trifluoromethyl- sulphonylamino, carboxy, 1H-tetrazol-5-yl, acetylamino or OR^{12} wherein R^{12} represents hydrogen, methyl, benzyl, $\text{CH}_2\text{CO}_2\text{H}$, CH_2CONH_2 , $\text{CH}_2\text{CONHCH}_3$, $\text{CH}_2\text{CON}(\text{CH}_3)_2$.

5



wherein the substituent is preferably in the meta- position) or an indole wherein the nitrogen atom is optionally substituted by the group $-\text{CH}_2\text{CO}_2\text{H}$ and the benzo ring is optionally substituted by chlorine, methyl, methoxy, nitro, hydroxy or amino; R^3 represents hydrogen, methyl, cyclohexyl, 2-fluorophenyl or phenyl or, more particularly, 2 fluorophenyl or phenyl; and X represents fluorine and z is 1 or, more particularly, X is hydrogen;

A particularly interesting class of compounds for use in the formulation according to the present invention because they exhibit a very high and selective affinity for the CCK-A receptor as well as exceptional efficacy are those wherein R^2 is an indole group. A preferred group of compounds within this class are those wherein the indole group is substituted on the nitrogen atom by the group $-\text{CH}_2\text{CO}_2\text{H}$ or, more preferably, the nitrogen atom is unsubstituted, and benzo ring of the indole group is optionally substituted by a group selected from chlorine, methyl, methoxy, nitro, hydroxy or amino.

A particularly preferred compound for use in the formulation according to the invention is :

25 1H-Indole-2-carboxylic acid {1-[Isopropyl-(4-methoxyphenyl)carbamoyl-methyl]-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl)-amide and enantiomers thereof.

As provided herein, the term alkyl is generally intended to mean both straight chain and branched chain aliphatic isomers of the corresponding alkyl. For example, C_{1-6} alkyl is intended to include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tertbutyl, n-pentyl, etc.

The term cycloalkyl, as provided herein, is intended to mean all alicyclic isomers of the corresponding alkyl. For example, the term C_{3-6} alkyl, as provided herein, is intended to include such groups as cyclopropyl, cyclopentyl and cyclohexyl.

The term halogen is intended to mean F, Cl, Br or I.

5 The term tetrazole as a group or part of a group refers to the (1 H)-tetrazol-5-yl grouping and tautomers thereof.

10 Those skilled in the art will recognize that stereocenters exist in compounds of Formula (I). Accordingly, the present invention includes all possible stereoisomers and geometric isomers of Formula (I) and includes not only racemic compounds but also the optically active isomers as well. When a compound of Formula (I) is desired as a single enantiomer, it may be obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or any convenient intermediate. Resolution of the final product, an intermediate or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Carbon Compounds by E. L. Eliel (Mcgraw Hill, 1962) and Tables of Resolving Agents by S. H. Wilen. Additionally, in situations where tautomers of the compounds of Formula (I) are possible, the present invention is intended to include all tautomeric forms of the compounds.

20 It will also be appreciated by those skilled in the art that the compounds of the present invention may also be utilized in the form of a pharmaceutically acceptable salt or solvate thereof. The physiologically acceptable salts of the compounds of Formula (I) include conventional salts formed from pharmaceutically acceptable inorganic or organic acids as well as quaternary ammonium acid addition salts. More specific examples of suitable salts include hydrochloric, hydrobromic, sulphuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, maleic, tartaric, citric, pamoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulphonic, methanesulphonic, naphthalene-2-sulphonic, benzenesulphonic and the like. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. References hereinafter to a compound for use in the invention include both compounds of Formula (I) and their pharmaceutically acceptable salts and solvates.

The compounds of formula (I) exhibit CCK-A agonist activity and can be considered full or partial cholecystokinin agonists in that they bind to CCK-A receptors and either fully or partially stimulate gallbladder contraction and/or reduce feeding in animal paradigms.

5

As agonists of CCK-A receptors, the compounds of formula (I) are useful anorectic agents advantageous in the treatment of obesity as well as related pathologies, such as diabetes or hypertension. Moreover, the compounds disclosed herein provide for new approaches for inducing satiety, providing for appetite regulation and modifying food intake in mammals, especially humans, to regulate appetite, treat obesity and maintain weight loss.

10

Additionally, certain compounds of formula (I) may also exhibit some antagonist activity at particular site-specific CCK-B and gastrin receptors as demonstrated by their inhibition of CCK-4 stimulated contraction of isolated guinea-pig ileum longitudinal muscle-myenteric plexus and pentagastrin-stimulated acid secretion in rat isolated gastric mucosa using the procedures described by M. Patel and C. F. Spraggs in Br. J. Pharmac., (1992), 106, 275-282 and by J. J. Reeves and R. Stables in Br. J. Pharmac., (1985), 86, 677-684.

15

20

The relative affinities of compounds of formula (I) for the CCK-A and CCK-B receptors may be determined using known conventional procedures such as described by Fornos et al J. Pharmacol Exp. Ther., 1992 261, 1056-1063.

25

The ability of compounds of formula (I) to inhibit gastric acid secretion, such as pentagastrin stimulated acid secretion may be determined in the conscious gastric fistula rat using methods described by Hedges and Parsons Journal of Physiology 1977, 267 191-194.

30

According to a further aspect of the present invention, there is provided herein a method for the treatment of a mammal, including man, in particular in the treatment conditions where modification of the effects of CCK and/or gastrin is of therapeutic benefit, the method comprising administering to the patient an enterically coated tablet or capsule containing a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof.

35

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms. Moreover, it will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses employed for adult human treatment will typically be in the range of 0.02 - 5000 mg per day, e.g., 1-1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

Compounds of general Formula (I), methods for their preparation and their activity as CCK-A agonists are described in WO9424149.

Example

The following example illustrates the invention but should not be construed as a limitation thereto.

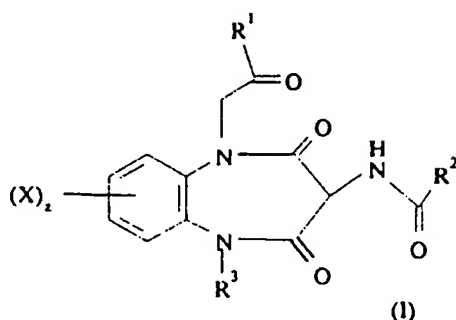
Tablet

Active Ingredient	50 mg
Lactose anhydrous USP	163 mg
Microcrystalline Cellulose NF	69 mg
Pregelatinized starch Ph. Eur.	15 mg
Magnesium stearate USP	3 mg
<hr/>	
Compression weight	300 mg

The active ingredient, microcrystalline cellulose, lactose and pregelatinized starch are sieved through a 500 micron sieve and blended in a suitable mixer. The magnesium stearate is sieved through a 250 micron sieve and blended with the active blend. The blend is compressed into tablets using suitable punches, then coated with cellulose acetate phthalate in a conventional manner.

Claims

1. A pharmaceutical formulation in solid dosage form for oral administration
5 which comprises a compound of Formula (1)



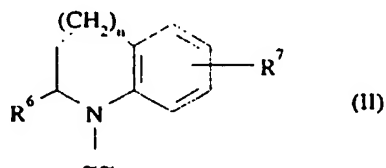
and physiologically salts and solvate thereof wherein:

10

X is either hydrogen, trifluoromethyl, alkyl, C₁₋₄alkylthio, -O(C₁₋₄alkyl) or halogen;

R¹ is either Formula II or -NR⁴R⁵;

15



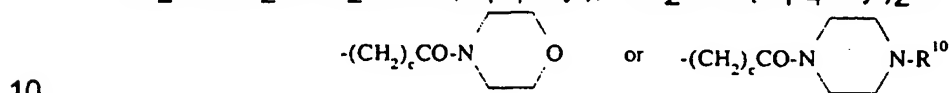
R² is either:

- (1) a heterocycle linked at its 2- position and selected from pyrrole,
20 tetrahydropyrrole, indole, benzofuran, thiophene, benzothiophene,
indoline, quinoline or 4-oxobenzopyran and wherein said pyrrole,
tetrahydropyrrole, indole or indoline may optionally be substituted on
the ring nitrogen thereof by the group R⁸ as defined hereunder and
said indole, indoline, quinoline, benzofuran, benzothiophene or 4-oxo-
25 benzopyran may optionally be substituted in the benzo ring thereof by
the group R⁹ as defined hereunder or

- (2) phenyl or phenyl mono- or disubstituted independently with halogen, hydroxy, cyano, carboxy, $-O(C_{1-4}alkyl)$, $-O(CH_2C_6H_5)$, $-COO(C_{1-4}alkyl)$, amino, dimethylamino, $-NHR^{10}$, 1-pyrrolidinyl or tetrazolyl; or
- 5 (3) pyridine or pyridinyl mono- or disubstituted independently with halogen, methyl, hydroxy, nitro, cyano, carboxy, $-O(C_{1-4}alkyl)$, $-O(CH_2C_6H_5)$, $-COO(C_{1-4}alkyl)$, amino or dimethylamino; or
- 10 (4) $-NHR^{11}$ where R^{11} is defined hereinunder or R^{11} is 7-indazolyl containing a group R^{10} at the N-1 position;
- R^3 is hydrogen, $C_{1-6}alkyl$, $C_{3-6}cycloalkyl$, phenyl or phenyl mono- or disubstituted independently with halogen;
- 15 R^4 is independently $C_{3-6}alkyl$, $C_{3-6}cycloalkyl$, $C_{3-6}alkenyl$, phenyl, $-(CH_2)_pCN$ or $-(CH_2)_pCOO(C_{1-4}alkyl)$ and R^5 is independently $C_{3-6}alkyl$, $C_{3-6}cycloalkyl$, $C_{3-6}alkenyl$, benzyl, phenyl or phenyl mono- or disubstituted independently with $C_{1-3}alkyl$, cyano, hydroxy, dimethylamino, $-O(C_{1-4}alkyl)$, $-O(CH_2C_6H_5)$, $-NH(C_{1-4}alkyl)$, $-COO(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$ pyrrolidino, morpholino or
- 20 halogen or R^4 is $C_{1-2}alkyl$ and R^5 is phenyl substituted at the 2- or 4- position with chloro, methyl, methoxy or methoxycarbonyl;
- R^6 is hydrogen or methyl;
- 25 R^7 is hydrogen, hydroxy, fluoro, dimethylamino, $-O(C_{1-4}alkyl)$ or $-O(CH_2C_6H_5)$;
- R^8 is $-(CH_2)_bCOOH$;
- R^9 is methyl, chloro, nitro, hydroxy, methoxy or $-NHR^{10}$;
- 30 R^{10} is hydrogen, acetyl, $C_{1-4}alkyl$, $-SO_3H$, $-SO_2CH_3$, $-SO_2CF_3$ or $-SO_2C_6H_5$, $C_{1-4}alkoxycarbonyl$;
- 35 R^{11} is phenyl or phenyl mono- or disubstituted independently with fluorine, trifluoromethoxy, $C_{1-4}alkylthio$, $-(CH_2)_cCOOH$, $-(CH_2)_cCOO(C_{1-4}alkyl)$, $-(CH_2)_cSCH_3$, $-(CH_2)_cSOCH_3$, $-(CH_2)_cSO_2CH_3$, $-(CH_2)_cCONH_2$, $-SCH_2COOH$, $-CONH(SO_2CH_3)$, $-CONH(SO_2CF_3)$, $-(CH_2)_cN(C_{1-4}alkyl)_2$, $-(CH_2)_cNH(SO_2CF_3)$, $-(CH_2)_cN(SO_2CF_3)(C_{1-4}alkyl)$, $-(CH_2)_cSO_2NHCO(C_{1-4}alkyl)$

4alkyl), $-(CH_2)_cSO_2N(C_{1-4}alkyl)CO(C_{1-4}alkyl)$, $-(CH_2)_cCONHSO_2(C_{1-4}alkyl)$,
 $-(CH_2)_cCON(C_{1-4}alkyl)SO_2(C_{1-4}alkyl)$, $-(CH_2)_cOR^{12}$ $-(CH_2)_cNHR^{10}$ or phenyl
 monosubstituted with $-(CH_2)_c(tetrazolyl)$, $-(CH_2)_c(carboxamidotetrazolyl)$ or -
 $(CH_2)_c(pyrrolidinyl)$ or R^{11} is selected from pyridine or pyridinyl mono- or
 5 disubstituted independently with halogen, methyl, hydroxy, nitro, cyano,
 carboxy, $-O(C_{1-4}alkyl)$, amino, dimethylamino, $-NHR^{10}$;

R^{12} is hydrogen, $C_{1-6}alkyl$, $C_{3-6}cycloalkyl$, $-CH_2C_6H_5$, $-CH_2COOH$, -
 CH_2CONH_2 , $-CH_2CONH(C_{1-4}alkyl)$, $-CH_2CON(C_{1-4}alkyl)_2$ or



z is 1 or 2;

n is 1 or 2;

15 p is an integer from 1-4;

b is an integer from 0-3; and

c is 0 or 1;

20

together with one or more pharmaceutically acceptable carriers wherein the
 formulation encased in an enteric coating or capsule.

2. A pharmaceutical composition as claimed in Claim 1 wherein R^1
 25 represents the group of Formula (II) wherein R^6 is methyl, R^7 is hydrogen,
 hydroxyl, methoxy or fluorine and n is 1 or R^1 represents the group NR^4R^5
 wherein R^4 represents $C_{3-6}alkyl$, cyclohexyl or phenyl, and R^5 represents C_{3-6}
 $alkyl$ or phenyl optionally substituted in the para position by hydroxy,
 dimethylamino, methoxy, fluorine, pyrrolidino or morpholino.

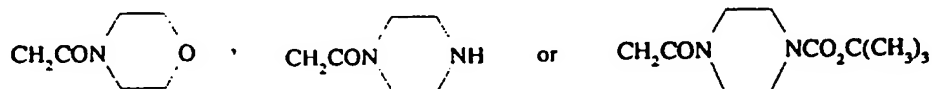
30

3. A pharmaceutical composition as claimed in Claims 1 or 2 wherein R^1
 represents the group NR^4R^5 and R^4 represents propyl or isopropyl and R^5
 represents phenyl or phenyl substituted in the para position by a group selected
 from hydroxy, methoxy, dimethylamino, fluorine, or morpholino.

35

4. A pharmaceutical composition as claimed in any of Claims 1 to 3
 wherein R^2 represents a group selected from phenyl (optionally substituted by

- one or two groups which may be the same or different and selected from chlorine, fluorine, amino, hydroxy or carboxy,) or NHR^{11} wherein R^{11} is phenyl (optionally substituted by fluoro, hydroxy, amino, dimethylamino, trifluoromethylsulphonylamino, C_{1-4} alkoxy carbonyl, carboxy, 1H-tetrazol-5-yl, acetylamino or OR^{12} wherein R^{12} represents hydrogen, methyl, benzyl, $\text{CH}_2\text{CO}_2\text{H}$, CH_2CONH_2 , $\text{CH}_2\text{CONHCH}_3$, $\text{CH}_2\text{CON}(\text{CH}_3)_2$



- for 7-indazolyl wherein the N-1 substituted is hydrogen, or R^2 represents an indole group wherein the nitrogen atom is optionally substituted by the group - $\text{CH}_2\text{CO}_2\text{H}$ and the benzo ring is optionally substituted by a group selected from chlorine, methyl, methoxy, nitro, hydroxy or amino.
5. A pharmaceutical composition as claimed in any of Claims 1-4 wherein R^2 represents an indole group which is unsubstituted on the nitrogen atom and in which the benzo ring thereof is optionally substituted by a group selected from chlorine, methyl, methoxy, nitro, hydroxy or amino.
6. A pharmaceutical composition as claimed in any of Claims 1-5 wherein R^3 represents hydrogen, methyl, cyclohexyl, 2-fluorophenyl or phenyl.
7. A pharmaceutical composition as claimed in any of Claims 1-6 wherein R^3 represents phenyl.
8. A pharmaceutical composition as claimed in any of Claims 1-7 wherein X represents hydrogen.
9. A pharmaceutical composition as claimed in Claim 1 wherein R^1 represents NR^4R^5 and R^4 represents isopropyl and R^5 represents p-methoxyphenyl; R^2 represents an unsubstituted 2-indole group; R^3 represents phenyl and X represents hydrogen and enantiomers thereof.
10. A pharmaceutical composition as claimed in claim 1 in the form of an enterically coated tablet.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/12829

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO,A,94 24149 (GLAXO INC.) 27 October 1994 cited in the application see page 11, line 7 ---	1-10
A	WO,A,93 14074 (GLAXO SPA) 22 July 1993 see page 9, line 12 - line 13 ---	1-10
Y	WO,A,90 06937 (ABBOTT LAB) 28 June 1990 cited in the application see page 175, paragraph 3 -----	1-10

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.*** Special categories of cited documents :**

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

30 January 1996

Date of mailing of the international search report

16.02.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Foerster, W

INTERNATIONAL SEARCH REPORT

information on patent family members

Int. Application No

PCT/US 95/12829

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9424149	27-10-94	AU-B- 6567594	08-11-94
		AU-B- 6567694	08-11-94
		CA-A- 2158972	27-10-94
		CA-A- 2158973	27-10-94
		WO-A- 9424151	27-10-94
		FI-A- 954852	12-10-95
		FI-A- 954853	12-10-95
		NO-A- 954090	13-12-95
		NO-A- 954091	13-12-95
WO-A-9314074	22-07-93	AP-A- 369	06-11-94
		AU-B- 661749	03-08-95
		AU-B- 3193593	22-07-93
		AU-B- 3450193	03-08-93
		BG-A- 98881	31-03-95
		CA-A- 2087672	22-07-93
		CN-A- 1074678	28-07-93
		CZ-A- 9401736	13-09-95
		EP-A- 0558104	01-09-93
		FI-A- 943421	19-07-94
		HU-A- 67375	28-03-95
		JP-A- 7118244	09-05-95
		NO-A- 942720	20-07-94
		NZ-A- 245715	26-07-95
		SK-A- 86494	08-03-95
		ZA-A- 9300375	18-07-94
WO-A-9006937	28-06-90	CA-A- 2006189	21-06-90
		EP-A- 0449884	09-10-91
		GR-A- 89100827	15-03-91
		US-A- 5270302	14-12-93